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Amiodarone Versus Placebo and Class Ic Drugs for Cardioversion of Recent-Onset Atrial Fibrillation: A Meta-Analysis

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OBJECTIVES This meta-analysis compared amiodarone with placebo and class Ic drugs for the cardioversion of recent-onset atrial fibrillation (AF), defined as lasting less than seven days.

BACKGROUND Despite the lack of trials that support its efficacy convincingly, amiodarone is widely used for conversion of recent-onset AF.

METHODS We searched Medline and EMBASE databases, as well as the Cochrane Controlled Trials Register for randomized trials on recent-onset AF comparing amiodarone to placebo or class Ic drugs. Data were combined according to a fixed effect model. The primary end point was the rate of conversion at 24 h. To study time-dependency of the drugs, efficacy at 1 to 2 h, 3 to 5 h, 6 to 8 h, and at 24 h was analyzed.

RESULTS We found six studies randomizing amiodarone versus placebo (595 patients) and seven studies versus class Ic drugs (579 patients). There was no significant difference between amiodarone and placebo at 1 to 2 h, but significant efficacy was found after 6 to 8 h (relative risk [RR] 1.23, $p = 0.022$) and at 24 h (RR 1.44, $p < 0.001$). Efficacy with amiodarone was inferior to class Ic drugs for up to 8 h (RR 0.67, $p < 0.001$) but no difference was seen at 24 h (RR 0.95, $p = 0.50$). There were no major adverse effects.

CONCLUSIONS Amiodarone is superior to placebo for cardioversion of AF, and even though the onset of conversion is delayed, its efficacy is similar at 24 h compared with class Ic drugs. These results favor amiodarone as a reasonable alternative for patients with recent AF in whom class Ic and other, more rapidly acting antiarrhythmic drugs cannot be used. (J Am Coll Cardiol 2003; 41:255–62) © 2003 by the American College of Cardiology Foundation

Termination of atrial fibrillation (AF) of recent onset, defined as onset within one week (1), is a major issue in daily clinical practice. The aim of prompt cardioversion is to improve functional status, to reduce atrial remodeling which may favor maintenance of arrhythmia, to reduce thromboembolic complications, and to reduce duration of hospitalization and hence cost.

Cardioversion may be achieved by either pharmacologic or electrical means. The success rate of electrical cardioversion varies between 70% and 90% (1). Immediate electrical cardioversion is indicated in patients with AF and a rapid ventricular response who have evidence of acute myocardial ischemia or symptomatic hypotension, angina, or heart failure that do not respond promptly to pharmacologic measures (1). Pharmacologic cardioversion may be otherwise attempted, thus avoiding the inconvenience of general anesthesia. For this purpose, class I and class III antiarrhythmic drugs have been studied. Class Ic drugs such as propafenone (2–5) and flecainide (6,7) have been shown to be efficacious. Among the class III agents, amiodarone was the first to have been used. The reported efficacy in converting AF is heterogeneous (8–13), and it has multiple extracardiac side effects. Its relatively good tolerance in the setting of heart failure and ischemic heart disease (14) contributes to the popularity of this drug. Although amiodarone is widely used to control AF, it is not approved in North America for any supraventricular arrhythmia. Our aim was to clarify by meta-analysis the role of amiodarone in the cardioversion of recent-onset AF. This drug was compared with placebo and with class Ic agents in randomized trials. The main outcome measure was restoration of sinus rhythm at 24 h.

METHODS

Search. We searched Medline and EMBASE databases (from 1967, with the last electronic search on October 18, 2001), as well as the Cochrane Controlled Trials Register for publications of randomized trials on cardioversion of AF by amiodarone compared with placebo or class Ic antiarrhythmic drugs. Language of publication did not influence article selection. References from these trials and from related review articles or editorials were checked for additional studies. Abstracts from the annual scientific meetings of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were overviewed from 1990 to 2001. Manufacturers were contacted. Authors of papers were contacted when specific data were unreported or ambiguous. Particular attention was paid to identify duplicate reports.

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Abbreviations and Acronyms
AF = atrial fibrillation
CI = confidence intervals
RR = relative risk

Inclusion and exclusion criteria. For inclusion, studies had to be prospective, randomized controlled trials of amiodarone versus placebo or versus a class Ic drug administered for cardioversion of recent-onset (≤1 week) AF. Both blinded and open-label trials were included.

Trials in the setting of atrial flutter or postoperative AF were excluded, as were those with active control groups (using, for example, digoxin or verapamil as a control drug). However, trials that used drugs such as digoxin for rate control only in both treatment arms were included.

End points. The primary end point was the rate of cardioversion within the first 24 h. The secondary end points were rates of cardioversion at 1 to 2 h, 3 to 5 h, and 6 to 8 h, mortality, proarrhythmia, and other adverse effects such as bradycardia, hypotension, and heart failure.

Data extraction. Trials selected for review were screened for information about patient characteristics, details of administration, treatment crossover, efficacy in converting to sinus rhythm, and adverse drug reactions. All data were extracted by one author (A.D.-D.) and checked by at least one other author independently. Authors agreed on extracted data by discussion.

Statistical analysis. Statistical analysis was done using the EasyMA program developed by one of the authors (M.C.). Analysis was made on an intention-to-treat basis. Relative risks (RR) and 95% confidence intervals (CI) were calculated. Individual RR were combined according to a fixed effect model, after having assessed for absence of heterogeneity by the Cochran *Q* test. In case of significant heterogeneity, a random effect model using Der Simonian and Laird method was used to combine the results. Methods based on odds ratio (Mantel-Haenszel and Peto methods) were also used, yielding similar results. Significance for association was inferred at the $p < 0.05$ level.

RESULTS

Trial selection. The different search strategies yielded 79 potentially relevant articles, 69 of which were subsequently excluded for various reasons. Twenty-eight studies had no control group and 32 compared amiodarone with a drug other than a Ic class or placebo. Of the remaining studies comparing amiodarone versus placebo or class Ic drugs, three were in the setting of postoperative AF, one was not randomized, and two studied AF lasting >7 days. One study randomized patients according to their date of birth and was not considered (15). Two studies (9,16) contained data from previously published reports (7,12). We considered only one original article (12) and one with a markedly larger cohort (9).

A total of 10 studies were thus included (8–13,17–20). Three studies were overlapping, that is, they compared amiodarone with class Ic drugs as well as with placebo (8,9,12). Six studies compared amiodarone with placebo (8–13) and included 595 patients (group 1). Seven studies compared amiodarone with a class Ic drug (8,9,11,12,17–20) and included 807 patients, of whom 579 were analyzed (group 2). The 228 patients excluded were from two studies (9,18) comparing several protocols for the administration of Ic drugs. Of these protocols, only intravenous propafenone was analyzed to prevent double-counting of the amiodarone patients and for more homogeneity. A study of patients with AF of less than two weeks duration was nevertheless included, as the mean duration of arrhythmia was only 24 h (17). Another study (8) included a minority of patients with postoperative AF and was included (results in this subgroup were comparable to those of the other patients). No dropouts were mentioned in any of the studies.

Patient characteristics. In each study, patients were matched as to age, gender, and duration of AF (Tables 1 and 2). Exclusion criteria were similar across the different studies and usually concerned severe heart failure, recent myocardial infarction, unstable angina, use of other antiarrhythmic drugs, severe conduction disturbances, thyroid dysfunction, hyperkalemia, and severe renal or hepatic insufficiency.

Use of beta-blockers and calcium channel antagonists was

Table 1. Characteristics of the Amiodarone Versus Placebo Studies

Study	No. of Patients (Amio/P)	Mean Age (yrs)	Gender (% Male)	AF Duration	Lone AF (Amio/P)	Blinding	Follow-Up (h)	Amiodarone
Boriani et al. (9)	51/121	58	55	≤7 days	20/54	Single	8	iv, 5 mg/kg bolus followed by 1.8 g/24 h
Cotter et al. (10)	50/50	66	43	<48 h	22/22	Single	24	iv, 125 mg/h (total 3 g)
Donovan et al. (8)	32/32	66	NA	≤72 h	NA	Double	8	iv, 7 mg/kg
Galve et al. (11)	50/50	60	55	<7 days	28/20	Single	24	iv, 5 mg/kg over 30 min followed by 1.2 g over 24 h
Kochiadakis et al. (12)	48/49	64	55	≤48 h	29/28	NA	24	iv, 300 mg over 1 h followed by 20 mg/kg/24 h and 1.8 g/day po
Peuhkurinen et al. (13)	31/31	59	73	<48 h	NA	Double	24	po, 30 mg/kg

AF = atrial fibrillation; Amio = amiodarone; iv = intravenous; Lone AF = atrial fibrillation without significant structural heart disease; NA = not available; P = placebo; po = orally.

Table 2. Characteristics of the Amiodarone Versus Class Ic Drugs Studies

Study	No. of Patients (Amio/Ic)	Mean Age (yrs)	Gender (% male)	AF Duration	Lone AF (Amio/Ic)	Blinding	Follow-up (h)	Amiodarone	Ic Drug
Propafenone									
Boriani et al. (9)	51/57	58	56	≤7 days	20/22	Single	8	iv, 5 mg/kg bolus followed by 1.8 g/24 h	iv, 2 mg/kg bolus followed by 0.0078 mg/kg/min
	51/119	58	57	≤7 days	20/50	Single	8	iv, 5 mg/kg bolus followed by 1.8 g/24 h	po, 600 mg in a single dose
Blanc et al. (17)	43/43	62	66	≤2 weeks	14/14	Single	48	po, 30 mg/kg in a single dose	po, 600 mg in a single dose
Kochiadakis et al. (12)	48/46	63	55	≤48 h	21/21	NA	24	iv, 300 mg over 1 h followed by 20 mg/kg/24 h and 1.8 g/day orally	iv, 2 mg/kg over 15 min followed by 10 mg/kg over 24 h
Negrini et al. (19)	30/31	59	47	≤7 days	16/18	Single	24	iv, 5 mg/kg over 10 min followed by 15 mg/kg over 24 h	iv, 2 mg/kg over 10 min followed by 10 mg/kg over 24 h
Martinez-Marcos et al. (18)	50/50	62	22	<48 h	NA	Single	12	iv, 5 mg/kg followed by 50 mg/h	iv, 2 mg/kg in 20 min followed by 1 mg/kg in 20 min if needed after 8 h
Treglia et al. (20)	27/27	57	43	<7 days	21/18	Single	48	iv, 5 mg/kg followed by 10 mg/kg/24 h	iv, 2 mg/kg followed by 5 mg/kg/24 h
Flecainide									
Boriani et al. (9)	51/69	59	56	≤7 days	20/27	Single	8	iv, 5 mg/kg over 30 s followed by 10–15 mg/min (total 5 mg/kg)	po, 300 mg in a single dose
Donovan et al. (8)	32/34	57	NA	≤72 h	NA	Double	8	iv, 7 mg/kg	iv, 2 mg/kg
Martinez-Marcos et al. (18)	50/50	59	25	<48 h	NA	Single	12	iv, 5 mg/kg followed by 50 mg/h	iv, 2 mg/kg in 20 min followed by 1 mg/kg if needed after 8 h

Abbreviations as in Table 1.

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Table 3. Efficacy of Amiodarone Versus Placebo in Converting AF to Sinus Rhythm at Various Time-Points

Study	Amio No. of Patients	Placebo No. of Patients	Conversion to Sinus Rhythm No. of Patients (%)					
			1–2 h		6–8 h		24 h	
			Amio	Placebo	Amio	Placebo	Amio	Placebo
Boriani et al. (9)	51	121	3 (6)	11 (9)	29 (57)	45 (37)	—	—
Cotter et al. (10)	50	50	3 (6)	1 (2)	31 (62)	29 (58)	46 (92)	32 (64)
Donovan et al. (8)	32	32	11 (34)	7 (22)	19 (59)	18 (56)	—	—
Galve et al. (11)	50	50	15 (30)	12 (24)	24 (48)	23 (46)	34 (68)	30 (60)
Kochiadakis et al. (12)	48	49	—	—	—	—	40 (83)	27 (55)
Peuhkurinen et al. (13)	31	31	4 (13)	1 (3)	16 (52)	6 (20)	27 (87)	11 (35)
Total n (%)	262	333	36 (17)	32 (11)	119 (56)	121 (43)	147 (82)	100 (56)

AF = atrial fibrillation; Amio = amiodarone.

permitted at randomization in two trials (8,10), as was digoxin in one trial (19). Digoxin was used to slow heart rate in three studies (10–12) when it exceeded 100/min. In one study (13), verapamil was used in the placebo group to slow the heart rate to below 100/min.

Strategies for anticoagulation (when reported) varied. Examples are inclusion of patients with AF of >72 h duration only if previous anticoagulation was given (9), and routine transesophageal echocardiography in all patients with AF > 48 h without previous anticoagulation (17).

Treatment regimens. The different drug dosages and schedules are detailed in Tables 1 and 2. Most trials reported intravenous administration of a loading dose followed by continuous infusion. Oral doses were most often single. For intravenous amiodarone, dosages varied from a 7 mg/kg loading dose to a continuous 24-h infusion totaling 3 g. The dose of oral amiodarone was 30 mg/kg administered during the first 24 h. Intravenous propafenone was administered as a 2 mg/kg intravenous bolus followed by a second dose of 1 mg/kg if needed, or an infusion of 5 to 10 mg/kg/24 h. Oral propafenone was given as a single 600-mg dose. For flecainide, a 2 mg/kg intravenous bolus or a 300-mg oral dose was administered.

Patient follow-up. Follow-up varied from 8 to 48 h (Tables 1 and 2). None of the studies in the amiodarone versus placebo group reported efficacy at 3 to 5 h. All patients were monitored by telemetry and blood pressure recordings.

Meta-analysis. RETURN OF SINUS RHYTHM. Amiodarone showed greater efficacy compared with placebo (Table 3, Fig. 1) at 6 to 8 h (RR 1.23, 95% CI 1.03 to 1.47, $p = 0.022$) and at 24 h (RR 1.44, 95% CI 1.24 to 1.66, $p < 0.001$). The drug showed no significant efficacy at 1 to 2 h (RR 1.23, 95% CI 0.77 to 1.96, $p = 0.39$). The incidence of spontaneous return of sinus rhythm must be emphasized, as it varied between 35% and 64% at 24 h (Table 3). Because of heterogeneity of results at 24 h, most probably owing to the study by Peuhkurinen et al. (13), we tested different random effects models which all gave the same results.

Class Ic drugs were more effective than amiodarone (Table 4, Fig. 2) at 1 to 2 h (RR 0.35, 95% CI 0.24 to 0.50, $p < 0.001$), at 3 to 5 h (RR 0.44, 95% CI 0.31 to 0.61, $p < 0.001$), and at 6 to 8 h (RR 0.57, 95% CI 0.57 to 0.80, $p < 0.001$). However, at 24 h both drugs were equally effective (RR 0.95, 95% CI 0.83 to 1.09, $p = 0.50$). Because of heterogeneity of the results at 1 to 2 h, random effects models were used and gave similar results. Robustness of our results was tested by sensitivity analysis. In group 1, after excluding the study by Peuhkurinen et al. (13), results were similar, other than for the 6- to 8-h time-point, when the difference between amiodarone and placebo was not significant (RR 1.14, 95% CI 0.99 to 1.41, $p = 0.073$). In group 2, the results were homogenous. The influence of route of administration was tested by excluding studies using oral amiodarone (13,17), with no difference in results.

SIDE EFFECTS. There were no deaths in any trials. Nonsustained ventricular tachycardia was reported in two patients in the amiodarone group (11,17) and in one patient given propafenone (17). A single episode of sustained ventricular tachycardia was observed in a patient receiving placebo (8). Because of the small number of events, analysis of the data was impossible. Four episodes of 1:1 atrial flutter were reported, three in patients receiving flecainide (9,18) and one in a patient on placebo (9). Other side effects, such as hypotension, bradycardia, and heart failure were inconsistently defined and reported and were thus impossible to analyze accurately. However, most of these adverse events (such as transient hypotension) were without consequence.

DISCUSSION

The main findings of our meta-analysis is that amiodarone facilitates conversion of recent-onset AF to sinus rhythm (with a 44% superiority in efficacy compared with placebo), but with a delay of 8 to 24 h until the onset of antiarrhythmic activity. This efficacy is comparable to that of class Ic agents at 24 h after drug administration, although Ic drugs showed a more rapid onset of action, with some effect already apparent at 1 to 2 h after administration.

The slower onset of cardioversion using amiodarone compared with class Ic drugs may have several explanations. First, the blood level of the active metabolite of amiodarone (desethylamiodarone) is still low 1 h after intravenous administration, whereas that of flecainide attains a therapeutic concentration at that time-point (8). Second, amiodarone has a complex pharmacokinetic profile with a mul-

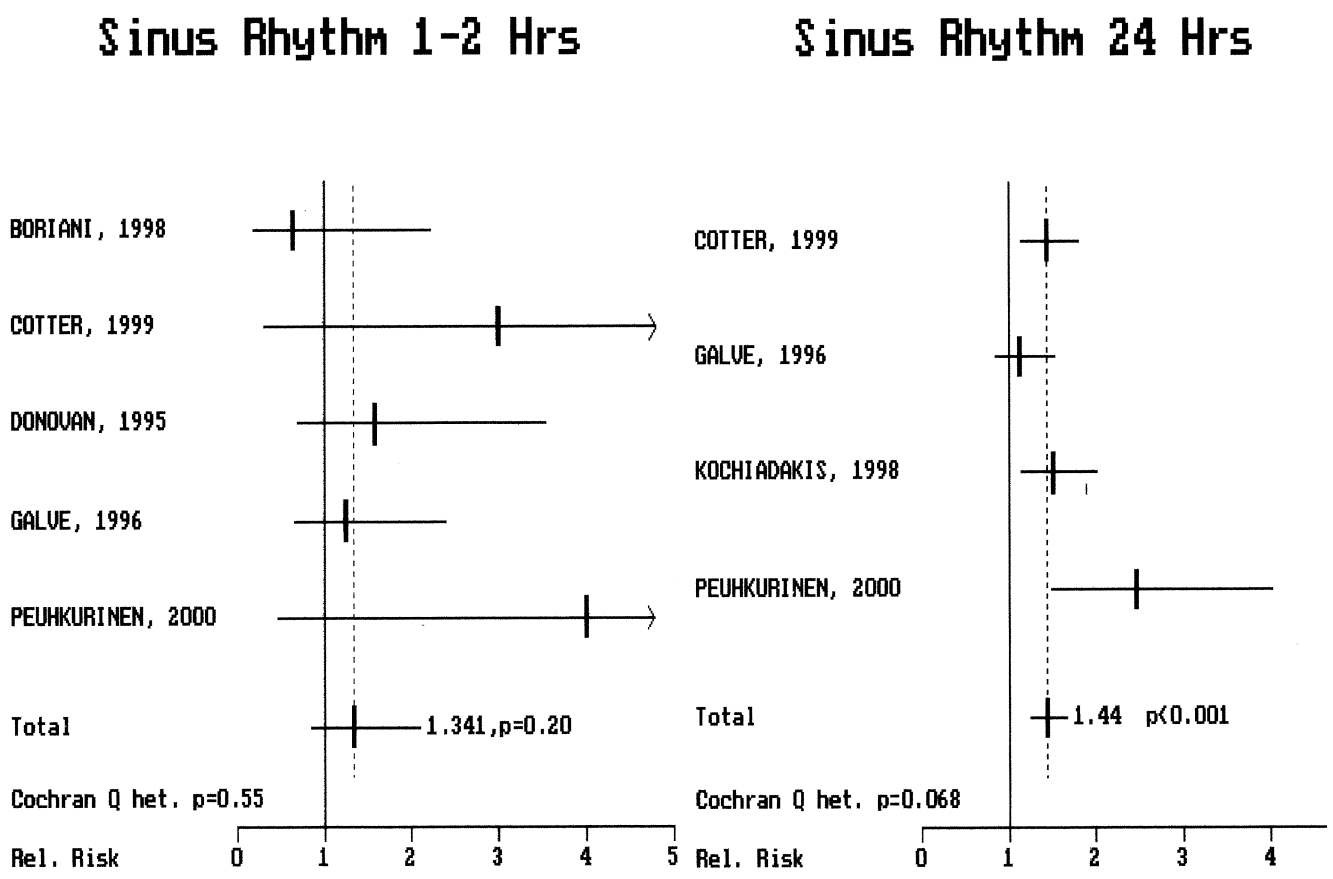

Figure 1. Amiodarone versus placebo showing no efficacy for return to sinus rhythm at 1 to 2 h **(left)** and efficacy at 24 h **(right).** Graphical representation shows relative risk and 95% confidence interval.

ticompartmental distribution and a long half-life, requiring more time for sufficient tissue impregnation (21). Third, the acute effect of amiodarone on atrial action potential duration is not well established (22), and the antiarrhythmic effect related to a prolonged refractory period may be retarded.

Even if cardioversion may be delayed compared with class Ic drugs, amiodarone has the advantage of promptly slowing a rapid ventricular rate (8,10,11,17). This may be due to predominant beta-adrenergic and calcium channel blockade observed early after intravenous amiodarone injection, the class III effect being least identifiable at this stage (21). Flecainide, on the other hand, shows little slowing of

Table 4. Efficacy of Amiodarone Versus Class Ic Drugs in Converting AF to Sinus Rhythm at Various Time-Points

Study	Amio No. of Patients	Placebo No. of Patients	Conversion to Sinus Rhythm No. of Patients (%)							
			1–2 h		3–5 h		6–8 h		24 h	
			Amio	Ic	Amio	Ic	Amio	Ic	Amio	Ic
Propafenone										
Boriani et al. (9)	51	57	3 (6)	22 (39)	13 (25)	33 (58)	29 (57)	46 (75)	—	—
		119		10 (8)		53 (45)		90 (76)		
Blanc et al. (17)	43	43	—	—	7 (16)	16 (37)	11 (26)	19 (44)	20 (47)	24 (56)
Kochiadakis et al. (12)	48	46	—	—	—	—	—	—	40 (83)	36 (78)
Negrini et al. (19)	30	31	6 (20)	18 (58)	10 (30)	20 (64)	12 (40)	22 (71)	24 (80)	27 (87)
Martinez-Marcos et al. (18)	50	50	7 (14)	30 (60)	—	—	21 (42)	34 (68)	—	—
Treglia et al. (20)	27	27	1 (4)	7 (26)	3 (15)	13 (65)	7 (26)	15 (55)	13 (48)	18 (67)
Flecainide										
Boriani et al. (9)	51	69	3 (6)	9 (13)	13 (25)	39 (56)	29 (57)	52 (75)	—	—
Donovan et al. (8)	32	34	11 (34)	20 (59)	—	—	19 (59)	23 (68)	—	—
Martinez-Marcos et al. (18)	50	50	7 (14)	29 (58)	—	—	21 (42)	41 (82)	—	—
Total	281*	526	28 (15)	139 (32)	23 (22)	174 (50)	99 (42)	301 (63)	97 (66)	104 (71)

*The amiodarone groups of the studies by Boriani et al. and Martinez-Marcos et al. are counted once.
Abbreviations as in Table 3.

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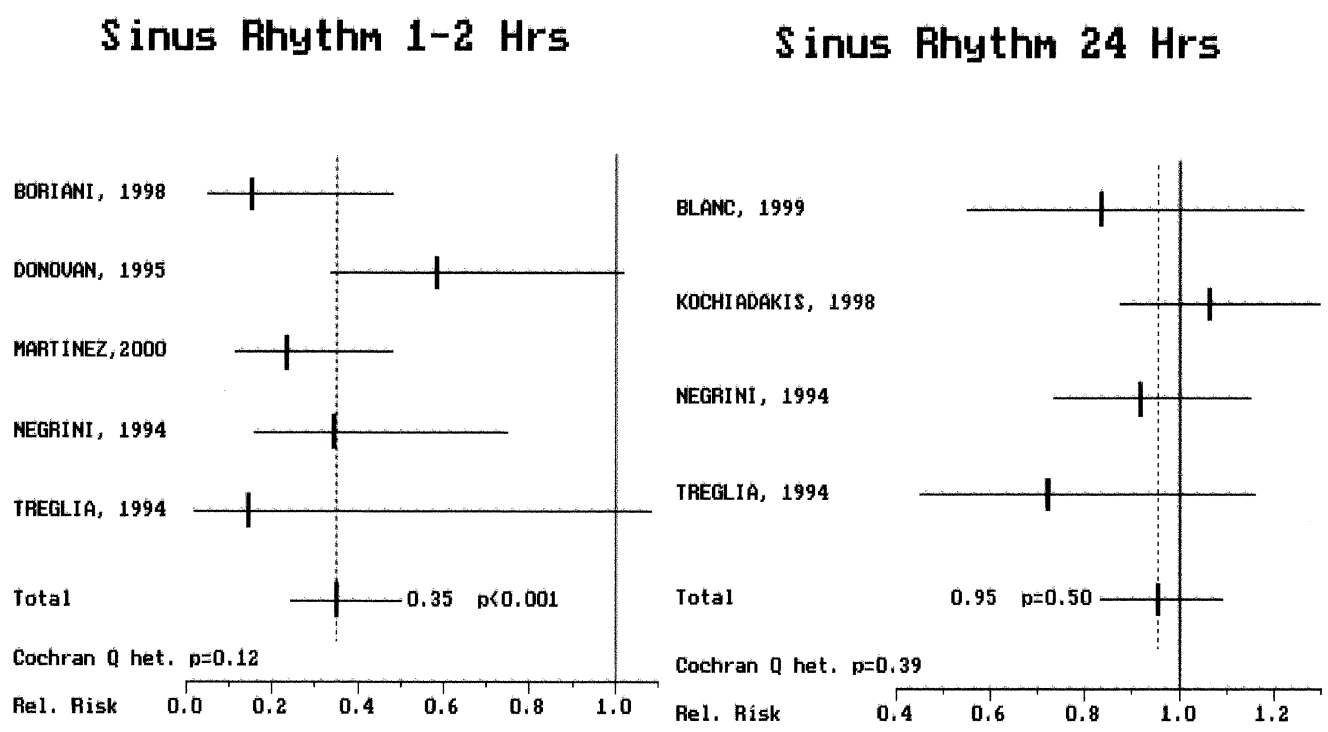

Figure 2. Amiodarone versus class Ic drugs showing a greater efficacy of class Ic drugs for return to sinus rhythm at 1 to 2 h **(left)** but no difference at 24 h **(right).** Graphical representation shows relative risk and 95% confidence interval.

atrioventricular nodal conduction. Furthermore, this compound has been shown to increase defibrillation thresholds, whereas amiodarone has been shown to enhance electrical cardioversion (23).

An alternative to amiodarone and class Ic drugs is ibutilide, which has the advantage of rapidly converting AF, making this a potentially useful drug in the emergency room setting. A placebo-controlled study including patients with a mean arrhythmia duration of about two weeks showed a 31% conversion rate with this drug (24). However, there was an 8.3% incidence of polymorphic ventricular tachycardia, which sometimes required electrical cardioversion. Dofetilide is another new class III antiarrhythmic agent that is effective in cardioverting AF (25). In a randomized trial comparing intravenous dofetilide with amiodarone and placebo in patients with AF of up to two months duration (26), dofetilide achieved a higher cardioversion rate than amiodarone and placebo (35%, 4%, and 4% of patients respectively). However, the follow-up period in that study was only 3 h, which may have been insufficient to show efficacy of amiodarone. Furthermore, 8% of the patients receiving dofetilide had torsade de pointes. These new class III agents are most useful for cardioverting atrial flutter, with efficacy rates of over 50% (24–26).

The issue of dosage and route of administration is difficult to assess, as protocols varied widely between studies. Intravenous amiodarone has greater bioavailability than the oral form, which is only 30% to 70% (21). It seems, furthermore, that intravenous and oral amiodarone do not have the same electrophysiologic effects, possibly owing to cumulative effects and/or active metabolites (27). After a brief high-dose oral load of amiodarone, the most pronounced prolongation of refractoriness is seen in the atrium (28). On the other hand, a single intravenous bolus dose has little impact on the atrial action potential duration and refractory period (29,30). In our meta-analysis, only one study used a single intravenous bolus dose of 7 mg/kg of amiodarone and did not show any efficacy in terminating AF (8). All the other studies employed a continuous infusion of the drug, usually preceded by a loading dose, resulting in a higher cumulative dose. Only two studies (13,17) used oral amiodarone with a single loading dose of 30 mg/kg, which was shown to be effective (13). Overall, it appears that there are no significant differences when the drug is used intravenously or orally, as long as a sufficient dose is administered. The total daily dose that may be given safely may be higher with the oral formulation because hypotension is usually not seen (21). Gastrointestinal side effects may, however, be problematic.

No serious side effects were reported with amiodarone. Class Ic drugs have the potential of inducing atrial flutter with 1:1 atrioventricular conduction, but this occurred only exceptionally (in three patients on flecainide). Thus, both amiodarone and class Ic drugs seem to be safe in the population studied. However, there is evidence that class I drugs may increase mortality in a subset of patients who may benefit most from cardioversion, i.e., those with severe underlying myocardial dysfunction or ischemic heart disease (31). Amiodarone should also be used with caution in these patients, as profound hypotension may be induced by intravenous (32) or high-dose oral loading (33). Adminis-

tration of the drug in critically ill patients has been reported to lead to severe bradycardia which may result in death (34). The incidence of extracardiac side effects due to short-term administration of amiodarone is not well defined. However, most of the toxicity of the drug seems to be dose-dependant and related to chronic treatment (35).

Limits of the meta-analysis. As with all meta-analyses, particular attention must be paid to the quality of the studies included. We included only prospective, randomized controlled studies. The time-points of analysis of efficacy varied between the studies, and it was necessary to define separate periods, resulting in a certain degree of heterogeneity. It might also seem difficult to compare studies with diverging results due to differences in study populations, drug dosage, and routes of administration. However, sensitivity analyses were done and showed robustness of our results. It must be emphasized that the results of the meta-analysis apply to the patient population studied, which consisted mostly of middle-aged patients without major underlying heart disease, and that about half of the population had lone AF. Finally, we were unable to accurately assess the incidence of side effects, as reporting was inconsistent across studies.

CONCLUSIONS

Our meta-analysis was aimed at defining the role of amiodarone in the conversion of recent-onset AF. The data show that this drug is effective compared with placebo and that even though the onset of conversion is delayed, efficacy is similar at 24 h compared with class Ic drugs. In clinical practice, amiodarone is a reasonable alternative to class Ic drugs and may be the drug of choice in the setting of ventricular dysfunction and ischemic heart disease if rapid cardioversion is not required. Most of the data are on intravenous amiodarone, and more studies using oral administration need to be done. Finally, the issues of optimal dosage and of out-patient treatment initiation should be assessed.

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